

# Subclinical cardiovascular disease and risk of incident frailty: The British Regional Heart Study

**Short running title:** Subclinical CVD and frailty

**Authors:** Douglas GJ McKechnie MBBS<sup>a</sup>, A Olia Papacosta MSc<sup>a</sup>, Lucy T Lennon MSc<sup>a</sup>,

Elizabeth A Ellins PhD<sup>b</sup>, Julian PJ Halcox MD<sup>b</sup>, Sheena E Ramsay PhD<sup>c</sup>, Peter H Whincup PhD

<sup>d</sup>, S Goya Wannamethee PhD<sup>a</sup>

<sup>a</sup> Department of Primary Care and Population Health, University College London, London, UK.

<sup>b</sup> Institute of Life Science, Swansea University, Swansea, UK.

<sup>c</sup> Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK.

<sup>d</sup> Population Health Research Institute, St George's University of London, London, UK.

**Corresponding author:** Dr Doug McKechnie, Department of Primary Care & Population Health, University College London, London NW3 2PF, UK

[douglas.mckechnie.11@ucl.ac.uk](mailto:douglas.mckechnie.11@ucl.ac.uk)

Twitter: @ldndoc

## Conflicts of interest

None to declare. A full list of DGJM's interests can be found at

<http://www.whopaysthisdoctor.org/doctor/500/active>.

## Funding

This work was supported by the British Heart Foundation (grant nos. RG/19/4/34452 and PG/09/024/26857). DGJM is an NIHR Academic Clinical Fellow, funded by Health Education England. The views expressed are those of the authors and not necessarily those of the NHS,

the NIHR or the Department of Health and Social Care. The funders had no role in the design and conduct of the study; collection, management, analysis, interpretation of the data; preparation, review, approval of or decision to publish the manuscript.

#### **Ethics approval**

The National Research Ethics Service Committee London.

**Word count of abstract** 300

**Word count of main paper** 3482

**Tables:** 3

**Figures:** 1

# **Abstract**

## **Background/Objectives**

Subclinical cardiovascular disease (CVD) is cross-sectionally associated with frailty, but the relationship between subclinical CVD and incident frailty has not been reported. We aimed to assess this prospective association.

## **Design**

Longitudinal analysis of data from the British Regional Heart Study, a prospective cohort study.

## **Participants**

1057 men, aged 71-92 years, robust or pre-frail at baseline, and without a clinical diagnosis of CVD.

## **Measurements**

Participants underwent baseline measurement of carotid-femoral pulse wave velocity (cfPWV), carotid intima-media thickness (CIMT), carotid distensibility coefficient (DC), and ankle-brachial pressure index (ABPI), and had questionnaire-based frailty assessment after three years. Frailty status was based on the Fried phenotype. Multivariate logistic regressions examined associations between incident frailty and tertile of cfPWV, CIMT, DC, and ABPI group ( $<0.9$ ,  $0.9-1.4$ ,  $\geq 1.4$ ).

## **Results**

865 men were examined and completed the 3 year follow-up questionnaire, of whom 78 became frail. Adjusted for age, prefrailty, body mass index, diabetes, smoking, atrial fibrillation, blood pressure, renal function, and incident CVD, higher CIMT was associated with greater odds of incident frailty (2<sup>nd</sup> tertile OR 1.62, 95% CI 0.78-3.35, 3<sup>rd</sup> tertile OR 2.61,

95% CI 1.30-5.23,  $p=0.007$ , trend  $p=0.006$ ). cfPWV showed a weaker, non-significant association (2<sup>nd</sup> tertile OR 1.79, 95% CI 0.85-3.78, 3<sup>rd</sup> tertile OR 1.73, OR 0.81-3.72,  $p=0.16$ , trend  $p=0.20$ ). There was no clear association between incident frailty and DC or ABPI. In subgroup analyses, CIMT was significantly associated with incident frailty in men  $\geq 80$  years (3<sup>rd</sup> tertile OR 6.99, 95%CI 1.42-34.5), but not in men aged 75-80 or  $<75$  years.

## **Conclusion**

Subclinical CVD, as measured by CIMT, is associated with greater risk of incident frailty in older men over three year follow-up, independent of the development of clinically-apparent stroke, heart failure, or myocardial infarction, and may be a modifiable risk factor for frailty. This association may be stronger in very old age.

## **Keywords**

Frailty; cardiovascular diseases; carotid intima-media thickness; aging; atherosclerosis; follow-up studies

## **Abbreviations**

ABPI: ankle-brachial pressure index; cfPWV: carotid-femoral pulse wave velocity; CIMT: Carotid intima-media thickness; DC: carotid distensibility coefficient

## Introduction

Frailty, an age-related multisystemic decline in physiological function, reserve, and resilience,(1) has a major impact on older individuals' health, and contributes significantly to the global burden of disease.(2) The pathogenesis of frailty is complex and multifactorial. Cardiovascular disease (CVD) has been linked with frailty at the epidemiological level and may share mechanistic determinants with frailty.(3) In a meta-analysis of 31,343 older people, frailty and pre-frailty were associated with greater risk of CVD in both cross-sectional and longitudinal analyses.(4) A more limited literature suggests the converse longitudinal relationship, CVD as a risk factor for the development of frailty, may exist.(5,6)

'Subclinical' CVD, detectable via non-invasive imaging modalities, is associated with higher mortality risk in older people (7), and has been cross-sectionally associated with frailty and aspects of the frailty phenotype(8–16). However, to our knowledge, a longitudinal association between subclinical CVD and incident frailty has not yet been described. Demonstrating such an association would further support the hypothesis that CVD and frailty are closely interrelated and can each lead to one another, and might help risk-stratify those at greatest risk of developing frailty as a potential target for intervention.

We therefore aimed to determine, in men without clinical evidence of prevalent CVD, prospective associations between subclinical CVD and the development of subsequent frailty, based on the Fried phenotype(17). Subclinical CVD was assessed by four methods:

carotid-femoral pulse wave velocity (cfPWV); carotid intima-media thickness (CIMT); carotid artery distensibility coefficient (DC); and ankle-brachial pressure index (ABPI).

## **Methods**

All data were obtained within the British Regional Heart Study, a prospective study of 7735 men, aged 40-59 at enrolment, drawn from 24 British towns and socioeconomically representative of those areas. Over 99% of participants were of White European ethnicity.<sup>(18)</sup> Initial screening occurred in 1978-90. A 30-year re-examination took place in 2010-12, with all 3137 surviving men invited to attend (now aged 71-92). Attendees completed a questionnaire, underwent physical examination, and provided a fasting blood sample. <sup>(19)</sup> Incident frailty status was obtained from a questionnaire performed three years later.

### **Questionnaire data**

Attendees of the 30-year examination completed a questionnaire regarding their lifestyle, medical, and medication history. Tobacco usage was divided into four categories: never smoked, long-term ex-smoker (stopped smoking  $\geq 10$  years prior), recent ex-smoker (stopped smoking  $< 10$  years prior), and current smokers.

### **Comorbidities**

The presence of prevalent and incident cardiovascular disease (myocardial infarction, stroke, or a diagnosis of 'heart failure') was taken from doctor's diagnoses, based on

primary care records and validated, where possible, with documentation from secondary care. Prevalent diabetes mellitus was defined as either a physician-confirmed diagnosis of diabetes mellitus, or a fasting serum glucose of greater than 7mmol/L. Polypharmacy was defined as taking five or more regular medications.(20)

### **Electrocardiography**

Twelve-lead electrocardiograms were recorded with a Siemens Sicard 460 instrument as part of the 30-year examination. Atrial fibrillation was diagnosed using the Minnesota Coding Scheme.(21)

### **Physical examination**

Blood pressure was measured with an Omron sphygmomanometer twice in the right arm, with the subject seated, the arm supported, and an appropriate cuff size used. Subjects were seated for approximately two minutes before measurements began. The mean of the two readings was used for analysis. With subjects in light clothing and without shoes, height was measured with a Harpenden stadiometer to the last complete 0.1 cm, and weight with a Tanita MA-418-BC body composition analyser (Tanita, Tokyo, Japan). Body mass index (BMI) was calculated as  $\text{weight}/(\text{height})^2$  ( $\text{kg}/\text{m}^2$ ). Grip strength was measured using a Jamar Hydraulic Hand Dynamometer. Three measurements were taken with each hand, and the best of six used for analysis. Walking speed over a 3 metre 'corridor' in a smooth-floored area was recorded. Chairs were positioned at each end of the corridor, with at least 0.5m separation from the ends to allow for acceleration and deceleration effects. Participants were asked to walk at their normal walking speed to the second chair, without rushing or



stopping, and could use their usual walking aids; participants that required assistance from another person to complete the walk were deemed unable to perform the test.

### **Blood measurements**

Glucose was measured in a fluoride oxidase plasma sample and creatinine measured using enzymatic colorimetric assays. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation. (22)

### **Non-invasive vascular markers**

Two technicians measured the non-invasive vascular markers in series. Images of the left and right carotid arteries were obtained with a 5-10 mHz linear probe using a Zone Ultra ultrasound system (Zonare Medical Systems, Mountain View, CA). Longitudinal images of the common carotid artery approximately 1 cm proximal to the carotid bifurcation and a cross-sectional sweep from the base of the common carotid artery to the mandible were recorded.

Using the Carotid Analyser software (Medical Imaging Applications, Iowa City, IA), CIMT (distance between the leading edge of the intima and the media-adventitia interface) and the peak systolic and end-diastolic common carotid artery diameter were measured. A 5-10 mm plaque-free area of interest, at least 1cm from the bifurcation, was selected from the longitudinal images. A mean CIMT was calculated from individual measurements obtained from the three end-diastolic images on each side.

Mean distension was calculated from the maximum and minimum carotid artery diameter assessed from three consecutive waveforms. Using these measurements, the distensibility coefficient (DC) was measured with the following formula:  $DC = [(2 \times \text{mean distension} / \text{baseline diameter}) / \text{mean pulse pressure (kPa)}] \times 1000$ .(23)

Carotid to femoral pulse wave velocity (cfPWV) was measured using a Vicorder device (Skidmore Medical, UK). An inflatable bladder attached to a neck collar was positioned over the right carotid pulse, and a Hokanson SC10 cuff was placed around the middle of the right thigh. cfPWV length was measured from the sternal notch to the centre of the thigh cuff. The cuffs were then simultaneously inflated. The pressure waveforms were visually assessed so that a minimum of 3 good quality waveforms were taken. Two recordings were taken with a difference in cfPWV  $\leq 0.5$  m/s and averaged.

Ankle-brachial pressure indices (ABPIs) were measured using a Vicorder device (Skidmore Medical, UK), in the right and left sides sequentially. Hokanson SC10 cuffs were positioned on the upper arm and lower leg (above the ankle). Photoplethysmography sensors were then clipped to the end of the middle finger and the great toe. Brachial and tibial arteries were occluded simultaneously, as the cuffs were inflated to 180mmHg. As the cuffs slowly deflated, the pulse data was visually assessed to minimise artefact from movement and to ensure that the blood pressures were taken at the point of the pulse returning at both sites. The Vicorder device provided blood pressures for both the brachial and ankle, and the ABPI ratio. Optimally, two measurements were recorded with a difference of  $\leq 5$  mmHg in either

the brachial or the ankle pressures, and the mean value used. If this could not be achieved, three measures were taken and averaged.

Reproducibility of the measurements was assessed in two ways: firstly, men from two study towns who had attended clinic visits were asked to return for a second visit approximately one year later, and the 123 participants who attended underwent repeat measurements under the same protocol as the first visit; secondly, both observers repeated an analysis of the ultrasound images from the first visit in 109 men to assess inter-observer reproducibility of CIMT and carotid distensibility measurement, and repeated their own analyses in 30 men to measure intra-observer reliability.(24)

Between-visit reproducibility was acceptable for all measurements (cfPWV coefficient of variation [CV]= 5.1%, DC CV= 12%, cIMT CV= 7.8%, ABPI CV= 0.65%), as was intra- and inter-observer reproducibility of the ultrasound measurements (cIMT inter-observer CV=7.1%, intra-observer CV=5.1%; carotid distension inter-observer CV=9.2%, intra-observer CV=11.9%).(24)

### **Frailty status**

Our definition of frailty was based on the Fried phenotype.(17) Five variables were calculated from the baseline examination, of which three were based on self-report: unintentional weight loss ( $\geq 5\%$  decrease in self-reported weight that respondents felt was unintentional); exhaustion (answering 'no' to the question 'Do you feel full of energy?'); low physical activity (self-report of being less active or much less active than an average man);

and two on objective measures: weakness (lowest fifth of grip strength distribution); and slow walking speed (lowest fifth of walking speed). Participants who took over 30 seconds to complete the 3 meter walk, or who were unable to complete the walk at all, were assigned to the 'slow walking speed' group. Where measured walking speed was unavailable, self-report of low walking pace was used (self-report of walking speed, or being unable to walk more than a few steps, or <200 yards, or difficulty walking across a room).

All living men were invited to complete a questionnaire three years later. Unintentional weight loss, exhaustion, and low physical activity were calculated in the same way. Slow walking speed was based entirely on self-report, as described above. Weakness was defined as self-report of 'fair' or 'poor' grip strength relative to men of the same age. Self-report of low gait speed and reduced grip strength have been shown to be associated – individually - with greater risk of incident disability and incident falls in this cohort, and a combined frailty score based on self-report performs as well as an objectively-measured Fried-based scoring system at predicting frailty-related adverse outcomes including incident disability, incident falls and mortality. (25)

In all cases, men with three or more features were defined as 'frail', those with one or two as 'pre-frail', and those with none as 'robust'.

### **Exclusion criteria**

Men with a prior diagnosis of myocardial infarction, stroke, and/or heart failure at baseline were excluded, as were those who were frail at baseline. Men who were missing all four subclinical CVS markers (DC, ABPI, cfPWV and CIMT) were excluded.

### **Statistical analysis**

All analyses were performed using version 9.4 of the SAS System for Windows (Cary, NC, USA). Statistical significance was set at  $p < 0.05$ . Descriptive statistics were used to report sample characteristics at baseline in men who did, and did not, develop frailty over the follow-up period. Comparisons between these groups were made using  $t$  tests for normally distributed continuous variables, and the chi-square test for categorical variables.

Given reports of a U-shaped relationship between BMI and frailty,(26) four BMI groups were calculated:  $<20\text{kg/m}^2$ ;  $20\text{--}24.9\text{kg/m}^2$ ;  $25\text{--}29.9\text{kg/m}^2$ , and  $\geq 30\text{kg/m}^2$ , with the  $20\text{--}24.9\text{kg/m}^2$  group used as the reference. Three groups were created for ABPI: low (one or both ABPIs  $<0.9$ ), normal (both ABPIs  $0.9\text{--}1.4$ ), and high (one or both ABPIs  $\geq 1.4$ ), based on the National Institute for Health and Care Excellence (NICE) guidelines, in which an ABPI  $<0.9$  indicates possible peripheral arterial disease, and an ABPI  $\geq 1.4$  potential arterial stiffening.(27) cfPWV, CIMT, and DC were subdivided into tertiles of each, with the lowest tertile used as the reference for cPWV and CIMT, and the highest as reference for DC.

Multivariate logistic regressions were performed, with incident frailty status at follow up (frail vs non-frail) as the dichotomous response variable. Separate analyses were conducted with cfPWV tertile, CIMT tertile, DC tertile, and ABPI group as categorical explanatory

variables. These were initially adjusted for age, then for age and frailty status at baseline (robust/prefrail), and then for additional potential confounders and/or mediators: BMI group, diabetes mellitus, smoking history, atrial fibrillation, use of blood pressure lowering medications, incident CVD (i.e. myocardial infarction and/or stroke and/or heart failure) between baseline and follow-up (all categorical variables), systolic blood pressure and estimated glomerular filtration rate (both continuous variables). To obtain a *p* value for the trend across groups, these analyses were repeated with cPWV/CIMT/DC tertile as ordinal explanatory variables.

To investigate for the presence of interactions, age- and pre-frailty-adjusted analyses were repeated, incorporating age\*[cfPWV/CIMT/DC tertile or ABI group] and prefrailty\*cfPWV/CIMT/DC tertile or ABI group] interaction terms. Further subgroup analyses proceeded to investigate significant interactions.

## Results

1722 men (55% of the surviving cohort) attended the baseline examination. 100 men lacked complete baseline frailty data and were excluded, as were an additional 303 men who were frail at baseline. 260 of the remainder were excluded due to CVD at baseline and a further 2 men due to missing data on all subclinical CVD parameters. Of the remaining 1057 men, 3-year follow-up data was available for 865 (82%), on whom the analyses below are based. 55 of the 192 men with missing follow-up data had died by the time of follow-up. A participant flow diagram is given in Fig. 1.

### Baseline characteristics and bivariate comparisons

Baseline characteristics of men who did, and did not, develop frailty at 3 year follow-up are given in Table 1. Compared to men who did not become frail, men who became frail were much more likely to have been pre-frail at baseline and were more likely to have developed a myocardial infarction or heart failure by the time of follow-up; they tended to be older and have lower diastolic blood pressures. Men who became frail were more likely to be in higher tertiles of cfPWV and CIMT than men who did not become frail, though there was no clear difference for DC or ABPI. None of the men who developed frailty had an ABPI of  $>1.4$  at baseline.

### Multivariate analyses

In multivariate analyses (Table 2), when adjusted for age and pre-frailty status, higher CIMT was associated with greater odds of incident frailty, compared to those in the first tertile of CIMT (2<sup>nd</sup> tertile OR 1.69, 95% CI 0.85-3.35,  $p=0.14$ , 3<sup>rd</sup> tertile OR 2.70, 95% CI 1.40-5.20,  $p=0.003$ , trend across groups  $p=0.002$ ). This was attenuated only slightly on adjustment for BMI group, diabetes mellitus, smoking history, atrial fibrillation, use of blood pressure lowering medications, incident myocardial infarction, heart failure and/or stroke between baseline and follow-up, systolic blood pressure and estimated glomerular filtration rate (2<sup>nd</sup> tertile OR 1.62, 95% CI 0.78-3.35,  $p=0.20$ , 3<sup>rd</sup> tertile OR 2.61, 95% CI 1.30-5.23,  $p=0.007$ , trend across groups  $p=0.006$ ).

There were weaker, non-statistically significant associations between higher cfPWV and greater odds of incident frailty (2<sup>nd</sup> tertile OR 1.86, 95% CI 0.92-3.77,  $p=0.08$ , 3<sup>rd</sup> tertile OR 1.76, 95% CI 0.87-3.57,  $p=0.12$ , trend across groups  $p=0.15$ ), which again weakened slightly on further adjustment (2<sup>nd</sup> tertile OR 1.79, 95% CI 0.85-3.78,  $p=0.13$ , 3<sup>rd</sup> tertile OR 1.73 95% CI 0.81-3.72,  $p=0.16$ , trend across groups  $p=0.20$ ). There were no clear associations between DC or ABPI and incident frailty.

### **Interactions**

There was a significant interaction between age, CIMT (tertiles) and incident frailty (formal test for interaction  $p=0.02$ ). No interaction was seen between age and other markers of subclinical atherosclerosis (cfPWV/DC/ABPI) with frailty. No statistically significant interaction was seen between prefrailty and markers of subclinical atherosclerosis and incident frailty.



The interaction between age and CIMT tertile was further explored by dividing the cohort into three age bands at baseline (<75 years, 75-80 years, ≥80 years) and repeating the fully-adjusted analyses within those groups (Table 3). There was a strong, statistically-significant association between higher CIMT and incident frailty in the ≥80 year group, but not in the other two age groups.

## Discussion

In a cohort of older British men, higher CIMT was associated with a greater risk of *de novo* frailty three years later, even after adjusting for pre-frailty, other clinical risk factors for CVD and frailty, and, importantly, the intervening development of clinically-apparent myocardial infarction, heart failure or stroke; this association appeared to be strongest in men aged 80 or greater. cfPWV showed a weaker, albeit non-statistically-significant, association with incident frailty risk, whereas DC and ABPI showed no clear association with the development of frailty.

Our findings extend the existing cross-sectional associations previously reported(8–16) by demonstrating a longitudinal association between subclinical CVD and incident frailty. To our knowledge, this is the first study to do so. Given additional evidence suggesting that clinically-apparent CVD is a risk factor for frailty, and vice versa,(28) it seems plausible that CVD and frailty share causal mechanisms. Inflammation, or ‘inflammaging’(29) may lead to the development of atherosclerosis, CVD and frailty, as might dysfunction of other physiological systems, such as haematopoiesis and coagulation(30). At the cellular level, oxidative stress and cellular senescence occur in both CVD and frailty. Emerging evidence suggests that novel biomarkers, such as growth differentiation factor 15, which is secreted in response to a wide range of cellular stresses, is associated with frailty in people with CVD, and may predict mortality after CVD events.(31) However, our results suggest that, whatever the mechanism, subclinical CVD does not lead to frailty solely via the intervening development of clinically-apparent cardiovascular disease.

We observed differing relationships between these four measures of subclinical CVD and incident frailty, with only CIMT showing a statistically significant positive association. DC, cfPWV and ABPI measures have all been associated with frailty features cross-sectionally(8,15,16), and it is possible that our sample size is too small to detect a statistically significant effect, meaning we cannot fully discount longitudinal associations with frailty. Arterial stiffness – as reflected by cfPWV and DC – is very closely linked to age and to hypertension(32,33), and our adjustments for those factors in multivariate analyses may explain the relative lack of association seen between arterial stiffness and incident frailty, although our findings are in keeping with other studies that have failed to clearly demonstrate an association between hypertension and incident frailty.(34) Furthermore, the anatomical site of measurement appeared to show differential associations with frailty: CIMT demonstrates structural changes to the wall of the carotid, and ABPI is mostly a measure of arterial stenosis in the peripheral arteries of the lower limbs.(35) Atherosclerosis of the carotid, and, potentially, cerebral, circulation may be more closely associated with incident frailty.

Whilst we accounted for multiple factors in our analyses, it is possible that significant unmeasured confounders remain. The intervening development, or presence, at baseline, of undiagnosed and/or 'silent' CVD is possible and could explain the association seen here. "Silent" cerebrovascular infarcts are common, even in healthy elderly people,(36) and have separately been associated with frailty(9) and with CIMT (37,38) (although not consistently(39,40)); men with higher CIMT may have had a higher silent infarct burden, leading to physical frailty. Subclinical cardiac ischaemia or heart failure may also have been

present, particularly given that there is often a significant delay between symptom onset and diagnosis in the latter case.(41)

There was evidence of effect modification within our study, with the association between incident frailty and higher CIMT tertile being strongest in men aged 80 or older at baseline. Robust over-80s with subclinical atherosclerosis may be at particularly high risk of progression to frailty. Stroke risk increases substantially with advancing age(42) and the combination of high CIMT and very old age may greatly increase the risk of infarcts, which might explain the pattern seen here. Over-80s with low CIMT might also be an unusually healthy group, and more likely to achieve 'successful aging'. Inferences from our subgroup analyses must be made with caution, however, given the small number of participants and incident frailty events in each subgroup; the estimates of effect size are very wide, and the lack of statistically-significant associations in the <75 and 75-80 age groups may be due to insufficient statistical power.

### **Strengths and limitations**

This study presents a novel longitudinal analysis of two important, and common, clinical conditions. It benefits from adjustment for multiple potential confounders. However, residual confounding may remain, including from factors discussed above. In particular, we lacked cardiac imaging (echocardiography or cardiac MRI) or brain imaging (CT/MRI) which may have demonstrated damage to those organs at baseline. Approximately 23% of the baseline sample was lost to follow-up, which may have introduced selection bias. The direction of effect of such bias can only be speculated, but it seems likely that men who were frail at follow up would be less able to respond than those in better health, and that

men who would have been frail might have been more likely to die before follow-up; this would have weakened any association seen here. The sample size may have been insufficient to allow detection of smaller associations, meaning we cannot fully discount associations between DC, ABPI and cfpWV and incident frailty, especially the latter, for which a positive but non-statistically significant association was seen. Finally, the cohort includes only white European men, and so generalisability to women and other ethnic groups is limited.

### **Implications for future study**

These findings should be replicated in other populations. Cardiac and cerebral imaging could be used to better stratify participants by demonstrating direct disease burden in those organs. Imaging markers of subclinical CVD, such as CIMT, could be investigated for their ability to predict frailty and risk-stratify those at highest risk for targeted intervention. Treatments for cardiovascular disease and atherosclerosis should be examined for any role in modifying, and perhaps reducing the risk of, frailty.

### **Conclusions**

This study provides evidence of an association between subclinical cardiovascular disease, as measured by carotid intima-media thickness, and the development of frailty over a three-year period, which was independent of incident clinically overt myocardial infarction, stroke or heart failure. This association was strongest in men over the age of 80. Imaging markers

of atherosclerosis at earlier stages showed limited, if any, association with incident frailty.

Subclinical CVD appears to be a risk factor for frailty.

## **Acknowledgements**

*Conflicts of interest:* The authors have no conflicts.

*Author contributions, using CRediT taxonomy:*

Douglas GJ McKechnie: Conceptualisation, methodology, software, formal analysis, writing - original draft

A Olia Papacosta: Software, formal analysis, investigation

Lucy T Lennon: Investigation, data curation, project administration

Elizabeth A Ellins: Methodology, investigation, writing- review and editing

Julian PJ Halcox: Methodology, investigation, writing – review and editing

Sheena E Ramsay: Writing – review and editing

Peter H Whincup: Writing – review and editing, funding acquisition

S Goya Wannamethee: Writing – review and editing, formal analysis, methodology, supervision, funding acquisition

*Sponsor's role:* The funders had no role in the design and conduct of the study; collection, management, analysis, interpretation of the data; preparation, review, approval of or decision to publish the manuscript.

## References

1. Clegg A, Young J. The Frailty Syndrome. *Clin Med (Lond)*. 2011;11(1):72-75. doi:10.7861/clinmedicine.11-1-72.
2. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *The Lancet*. 2019;394(10206):1365-1375. doi:10.1016/S0140-6736(19)31786-6.
3. Afilalo J. Frailty in Patients with Cardiovascular Disease: Why, When, and How to Measure. *Curr Cardiovasc Risk Rep*. 2011;5(5):467-472. doi:10.1007/s12170-011-0186-0.
4. Veronese N, Cereda E, Stubbs B, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. *Ageing Research Reviews*. 2017;35:63-73. doi:10.1016/j.arr.2017.01.003.
5. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: Emergence and Consequences in Women Aged 65 and Older in the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society*. 2005;53(8):1321-1330. doi:10.1111/j.1532-5415.2005.53405.x.
6. Keeney T, Fox AB, Jette DU, Jette A. Functional Trajectories of Persons with Cardiovascular Disease in Late Life. *Journal of the American Geriatrics Society*. doi:10.1111/jgs.15584.
7. Odden MC, Yee LM, Arnold AM, et al. Subclinical Vascular Disease Burden and Longer Survival. *J Am Geriatr Soc*. 2014;62(9):1692-1698. doi:10.1111/jgs.13018.
8. Ochi M, Kohara K, Tabara Y, et al. Arterial stiffness is associated with low thigh muscle mass in middle-aged to elderly men. *Atherosclerosis*. 2010;212(1):327-332. doi:10.1016/j.atherosclerosis.2010.05.026.
9. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of Subclinical Cardiovascular Disease With Frailty. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M158-M166. doi:10.1093/gerona/56.3.M158.
10. Yamanashi H, Kulkarni B, Edwards T, et al. Association between atherosclerosis and handgrip strength in non-hypertensive populations in India and Japan. *Geriatrics & Gerontology International*. 2018;18(7):1071-1078. doi:https://doi.org/10.1111/ggi.13312.
11. Campos AM, Moura FA, Santos SN, Freitas WM, Sposito AC. Sarcopenia, but not excess weight or increased caloric intake, is associated with coronary subclinical atherosclerosis in the very elderly. *Atherosclerosis*. 2017;258:138-144. doi:10.1016/j.atherosclerosis.2017.01.005.



12. Coelho Júnior HJ, Aguiar S da S, Gonçalves I de O, et al. Sarcopenia Is Associated with High Pulse Pressure in Older Women. *J Aging Res.* 2015;2015. doi:10.1155/2015/109824.
13. Xue Q, Qin M, Jia J, Liu J, Wang Y. Association between frailty and the cardio-ankle vascular index. *Clin Interv Aging.* 2019;14:735-742. doi:10.2147/CIA.S195109.
14. Park J, Park J-H, Park H. Association Between Carotid Artery Intima-Media Thickness and Combinations of Mild Cognitive Impairment and Pre-Frailty in Older Adults. *International Journal of Environmental Research and Public Health.* 2019;16(16):2978. doi:10.3390/ijerph16162978.
15. Orkaby AR, Lunetta KL, Sun FJ, et al. Cross-Sectional Association of Frailty and Arterial Stiffness in Community-Dwelling Older Adults: The Framingham Heart Study. *J Gerontol A Biol Sci Med Sci.* 2019;74(3):373-379. doi:10.1093/gerona/gly134.
16. Nadruz W, Kitzman D, Windham BG, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. *J Gerontol A Biol Sci Med Sci.* 2017;72(7):958-964. doi:10.1093/gerona/glw199.
17. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146-M157. doi:10.1093/gerona/56.3.M146.
18. Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. *Br Med J (Clin Res Ed).* 1981;283(6285):179-186.
19. Lennon LT, Ramsay SE, Papacosta O, Shaper AG, Wannamethee SG, Whincup PH. Cohort Profile Update: The British Regional Heart Study 1978–2014: 35 years follow-up of cardiovascular disease and ageing. *Int J Epidemiol.* 2015;44(3):826-826g. doi:10.1093/ije/dyv141.
20. Masnoon N, Shakib S, Kalisch-Ellett L, Cughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr.* 2017;17. doi:10.1186/s12877-017-0621-2.
21. Prineas RJ, Crow RS, Zhang Z-M. *The Minnesota Code Manual of Electrocardiographic Findings.* 2nd ed. edition. London: Springer; 2009. ISBN:978-1-84882-777-6.
22. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130(6):461-470. doi:10.7326/0003-4819-130-6-199903160-00002.
23. Dijk JM, Algra A, van der Graaf Y, Grobbee DE, Bots ML, SMART study group. Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. *Eur Heart J.* 2005;26(12):1213-1220. doi:10.1093/eurheartj/ehi254.

24. Ellins EA, Smith KE, Lennon LT, et al. Arterial pathophysiology and comparison of two devices for pulse wave velocity assessment in elderly men: the British regional heart study. *Open Heart*. 2017;4(2):e000645. doi:10.1136/openhrt-2017-000645.
25. Papachristou E, Wannamethee SG, Lennon LT, et al. Ability of Self-Reported Frailty Components to Predict Incident Disability, Falls, and All-Cause Mortality: Results From a Population-Based Study of Older British Men. *J Am Med Dir Assoc*. 2017;18(2):152-157. doi:10.1016/j.jamda.2016.08.020.
26. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, Body Mass Index, and Abdominal Obesity in Older People. *J Gerontol A Biol Sci Med Sci*. 2010;65A(4):377-381. doi:10.1093/gerona/glp186.
27. Assessment | Diagnosis | Peripheral arterial disease | CKS | NICE.  
<https://cks.nice.org.uk/topics/peripheral-arterial-disease/diagnosis/assessment/>. Accessed December 3, 2020.
28. Veronese N. Frailty as Cardiovascular Risk Factor (and Vice Versa). In: Veronese N, ed. *Frailty and Cardiovascular Diseases : Research into an Elderly Population*. Advances in Experimental Medicine and Biology. Cham: Springer International Publishing; 2020:51-54. doi:10.1007/978-3-030-33330-0\_6.
29. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology*. 2018;14(10):576-590. doi:10.1038/s41574-018-0059-4.
30. Stewart R. Cardiovascular Disease and Frailty: What Are the Mechanistic Links? *Clin Chem*. 2019;65(1):80-86. doi:10.1373/clinchem.2018.287318.
31. Sanchis J, Ruiz V, Bonanad C, et al. Growth differentiation factor 15 and geriatric conditions in acute coronary syndrome. *International Journal of Cardiology*. 2019;290:15-20. doi:10.1016/j.ijcard.2019.05.034.
32. Benetos A, Waeber B, Izzo J, et al. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. *American Journal of Hypertension*. 2002;15(12):1101-1108. doi:10.1016/S0895-7061(02)03029-7.
33. Mitchell GF. Arterial Stiffness and Hypertension: Chicken or Egg? *Hypertension*. 2014;64(2):210-214. doi:10.1161/HYPERTENSIONAHA.114.03449.
34. Vetrano DL, Palmer KM, Galluzzo L, et al. Hypertension and frailty: a systematic review and meta-analysis. *BMJ Open*. 2018;8(12):e024406. doi:10.1136/bmjopen-2018-024406.
35. Khan TH, Farooqui FA, Niazi K. Critical Review of the Ankle Brachial Index. *Curr Cardiol Rev*. 2008;4(2):101-106. doi:10.2174/157340308784245810.
36. Vermeer SE, Longstreth WT, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6(7):611-619. doi:10.1016/S1474-4422(07)70170-9.

37. Manolio Teri A., Burke Gregory L., O'Leary Daniel H., et al. Relationships of Cerebral MRI Findings to Ultrasonographic Carotid Atherosclerosis in Older Adults. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1999;19(2):356-365. doi:10.1161/01.ATV.19.2.356.
38. Vermeer SE, Den Heijer T, Koudstaal PJ, et al. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke*. 2003;34(2):392-396. doi:10.1161/01.str.0000052631.98405.15.
39. Longstreth WTJ, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar Infarcts Defined by Magnetic Resonance Imaging of 3660 Elderly People: The Cardiovascular Health Study. *Archives of Neurology*. 1998;55(9):1217-1225.
40. Longstreth WT, Dulberg, Manolio TA, et al. Incidence, Manifestations, and Predictors of Brain Infarcts Defined by Serial Cranial Magnetic Resonance Imaging in the Elderly. *Stroke*. 2002;33(10):2376-2382. doi:10.1161/01.STR.0000032241.58727.49.
41. Hayhoe B, Kim D, Aylin PP, Majeed FA, Cowie MR, Bottle A. Adherence to guidelines in management of symptoms suggestive of heart failure in primary care. *Heart*. 2019;105(9):678-685. doi:10.1136/heartjnl-2018-313971.
42. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *The Lancet Neurology*. 2003;2(1):43-53. doi:10.1016/S1474-4422(03)00266-7.

**Table 1: Characteristics of study population at baseline and bivariate comparisons.**

	Did not develop frailty (n=787)	Developed frailty (n=78)	<i>p value</i>
Age (years)	77.5 (4.1)	79.7 (5.0)	<0.001
<b>Pre-frail at baseline</b>	456 (58%)	72 (92%)	<0.001
<b>Smoking status</b>			
Never smoked	331 (42%)	28 (36%)	0.20
Recent ex-smoker	403 (51%)	40 (51%)	
Long-term ex-smoker	31 (4%)	5 (6%)	
Current smoker	22 (3%)	5 (6%)	
<b>Comorbidities</b>			
Atrial fibrillation at baseline	47 (6%)	5 (6%)	0.86
Diabetes mellitus at baseline	103 (13%)	15 (19%)	0.14
Taking blood pressure lowering drugs	365 (46%)	44 (56%)	0.09
Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> )	75.4 (15.8)	74.6 (20.1)	0.69
Developed myocardial infarction between baseline and follow up	6 (1%)	4 (5%)	0.01
Developed heart failure between baseline and follow up	10 (1%)	4 (5%)	<0.001
Developed stroke between baseline and follow up	9 (1%)	2 (3%)	0.29
Taking five or more regular medications	222 (28%)	27 (35%)	0.23
<b>Physical measurements</b>			
Systolic blood pressure (mmHg)	147 (18)	148 (20)	0.57
Diastolic blood pressure (mmHg)	77.7 (11)	74.9 (12)	0.04
BMI <20kg/m <sup>2</sup>	11 (1%)	4 (5%)	<0.001
BMI 20-24.9kg/m <sup>2</sup>	229 (29%)	20 (26%)	
BMI 25-29.9kg/m <sup>2</sup>	408 (52%)	38 (49%)	
BMI ≥30kg/m <sup>2</sup>	139 (18%)	16 (21%)	
<b>Markers of subclinical atherosclerosis</b>			
1 <sup>st</sup> tertile cfPWV (<9.5m/s)	269 (36%)	13 (19%)	0.02
2 <sup>nd</sup> tertile cfPWV (9.5-10.8m/s)	241 (32%)	26 (38%)	
3 <sup>rd</sup> tertile cfPWV (≥10.8m/s)	237 (32%)	29 (43%)	
1 <sup>st</sup> tertile CIMT (<0.73mm)	272 (35%)	14 (18%)	0.002
2 <sup>nd</sup> tertile CIMT (0.73-0.83mm)	264 (34%)	25 (32%)	
3 <sup>rd</sup> tertile CIMT (≥0.84mm)	249 (32%)	38 (49%)	
1 <sup>st</sup> tertile DC (<10.4x10 <sup>-3</sup> kPa)	253 (32%)	30 (38%)	0.53
2 <sup>nd</sup> tertile DC (10.4-13.6 x10 <sup>-3</sup> kPa)	262 (34%)	25 (32%)	
3 <sup>rd</sup> tertile DC (≥13.6 x10 <sup>-3</sup> kPa)	266 (34%)	23 (29%)	
ABPI <0.8	161 (21%)	20 (28%)	0.19
ABPI 0.8-1.4	577 (76%)	51 (72%)	
ABPI ≥1.4	19 (3%)	0	

BMI= body mass index, cfPWV= carotid-femoral pulse wave velocity, CIMT= carotid intimal media thickness, DC= distensibility coefficient, ABPI= ankle-brachial pressure index

**Table 2: Associations between subclinical cardiovascular disease and incident frailty in multivariate logistic regression analyses.**

	Age-adjusted OR for incident frailty (95% CI)	Model 1			Model 2		
		OR for incident frailty (95% CI)	<i>p</i> value	<i>p</i> value for trend	OR for incident frailty (95% CI)	<i>p</i> value	<i>p</i> value for trend
Carotid-femoral pulse wave velocity <sup>1</sup>							
1 <sup>st</sup> tertile ( $<9.5\text{m/s}$ )	1	1	-	0.15	1	-	0.20
2 <sup>nd</sup> tertile ( $9.5\text{-}10.8\text{m/s}$ )	2.01 (1.01- 4.03)	1.86 (0.92- 3.77)	0.08		1.79 (0.85- 3.78)	0.13	
3 <sup>rd</sup> tertile ( $\geq 10.8\text{m/s}$ )	2.00 (0.99- 4.02)	1.76 (0.87- 3.57)	0.12		1.73 (0.81- 3.72)	0.16	
Carotid intima media thickness <sup>2</sup>							
1 <sup>st</sup> tertile ( $<0.73\text{mm}$ )	1	1	-	0.002	1	-	0.006
2 <sup>nd</sup> tertile ( $0.73\text{-}0.83\text{mm}$ )	1.79 (0.91- 3.54)	1.69 (0.85- 3.35)	0.14		1.62 (0.78- 3.35)	0.20	
3 <sup>rd</sup> tertile ( $\geq 0.84\text{mm}$ )	2.56 (1.34- 4.88)	2.70 (1.40- 5.20)	0.003		2.61 (1.30- 5.23)	0.007	
Carotid artery distensibility coefficient <sup>3</sup>							
1 <sup>st</sup> tertile ( $<10.4\times 10^{-3}\text{ kPa}$ )	0.97 (0.53- 1.78)	0.88 (0.48- 1.63)	0.69	0.70	0.81 (0.41- 1.59)	0.54	0.54
2 <sup>nd</sup> tertile ( $10.4\text{-}13.6\times 10^{-3}\text{ kPa}$ )	0.94 (0.51- 1.71)	0.89 (0.48- 1.65)	0.71		0.91 (0.48- 1.75)	0.78	
3 <sup>rd</sup> tertile ( $\geq 13.6\times 10^{-3}\text{ kPa}$ )	1	1	-		1	-	
Ankle-brachial pressure index <sup>4</sup>							
$<0.8$	1.39 (0.80- 2.41)	1.29 (0.74- 2.26)	0.37		1.27 (0.68- 2.35)	0.46	
0.8-1.4	1	1	-		1	-	

OR= odds ratio, 95% CI = 95% confidence interval

Model 1: adjusted for age and frailty status at baseline. Model 2: additionally adjusted for BMI group, diabetes mellitus, smoking history, atrial fibrillation, use of blood pressure lowering medications, incident myocardial infarction, heart failure and/or stroke between baseline and follow-up, systolic blood pressure and estimated glomerular filtration rate.

<sup>1</sup> age-adjusted and Model 1: n=815; Model 2: n=777

<sup>2</sup> age-adjusted and Model 1: n=862; Model 2: n=819

<sup>3</sup> age-adjusted and Model 1: n=859; Model 2: n=817

<sup>4</sup> age-adjusted and Model 1: n=828; Model 2: n=789. Numbers for ABPI >1.4 extremely small so OR not presented here.

**Table 3: Associations between carotid intima media thickness and incident frailty by age group.**

Carotid intima media thickness tertile	75 years or younger (n=267, 16 incident frailty cases)		Between 75 and 80 years (n=323, 22 incident frailty cases)		80 years or older (n=229, 35 incident frailty cases)	
	OR for incident frailty* (95% CI)	p value	OR for incident frailty* (95% CI)	p value	OR for incident frailty* (95% CI)	p value
1 <sup>st</sup> tertile (<0.73mm)	1	-	1	-	1	-
2 <sup>nd</sup> tertile (0.73-0.83mm)	0.54 (0.12-2.55)	0.44	1.40 (0.46-4.30)	0.55	<b>5.49 (1.07-28.3)</b>	<b>0.04</b>
3 <sup>rd</sup> tertile (≥0.84mm)	1.92 (0.54-6.79)	0.31	1.49 (0.45-4.98)	0.52	<b>6.99 (1.42-34.5)</b>	<b>0.02</b>

\*adjusted for age, pre-frailty, BMI group, diabetes mellitus, smoking history, atrial fibrillation, use of blood pressure lowering medications, incident myocardial infarction, heart failure and/or stroke between baseline and follow-up, systolic blood pressure and estimated glomerular filtration rate. **Bold** = statistically significant association.